Stuart, B., Brotherwood, H., Van't Hoff, C., Brown, A., Van den Bruel, A., Hay, A. D., Moore, M. V., & Little, P. (2020). Exploring the appropriateness of antibiotic prescribing for common respiratory tract infections in UK primary care. *Journal of Antimicrobial Chemotherapy*, *75*(1), 236–242. https://doi.org/10.1093/jac/dkz410

Peer reviewed version

Link to published version (if available):
10.1093/jac/dkz410

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Oxford University Press at https://academic.oup.com/jac/article/75/1/236/5602187?searchresult=1. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/

OXFORD UNIVERSITY PRESS | Journal of Antimicrobial Chemotherapy

Exploring the appropriateness of antibiotic prescribing for common respiratory tract infections in UK primary care

Journal:	*Journal of Antimicrobial Chemotherapy*
Manuscript ID	JAC-2019-0961.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	13-Aug-2019
Complete List of Authors:	Stuart, Beth; University of Southampton, Primary Care and Population Sciences Brotherwood, Hannah; University of Southampton, Primary Care and Population Sciences van't Hoff, Catherine; University of Southampton Faculty of Medicine, Primary Care and Population Sciences Brown, Alastair; University of Southampton, Primary Care and Population Sciences Van den Bruel, Ann; KU Leuven, Academic Centre for Primary Care Hay, Alastair D; University of Bristol, Department of Community Based Medicine Moore, Michael; University of Southampton, PCPS Little, P.; University of Southampton, Primary Medical Care
Keywords:	Antibiotics, Prescribing practice, Primary care, Infection

SCHOLARONE™
Manuscripts

Exploring the appropriateness of antibiotic prescribing for common respiratory tract infections in UK primary care

Beth STUART[1*], Hannah BROTHERWOOD[1], Catherine VAN'T HOFF[1], Alastair BROWN[1], Ann VAN DEN BRUEL[3], Alastair D HAY[4], Michael MOORE[1] and Paul LITTLE[1]

1. *University of Southampton, Primary Care Medical Group, PCPS Unit, Aldermoor Health Centre, Southampton, UK*
2. *Academic Centre for Primary Care, KU Leuven, Leuven, Belgium*
3. *Centre for Academic Primary Care, Bristol Medical School: Population Health Sciences, University of Bristol, UK*

Corresponding author: Dr Beth Stuart, bls1@soton.ac.uk, telephone: +44 23 8059 1759

Confidential: For Peer Review only

Synopsis

Objective: To use illness severity scores to evaluate the appropriateness of antibiotic prescribing in United Kingdom general practice

Methods: To describe variations in practice prescribing rates, taking account of illness severity. We used three scores in three studies to measure severity: 'FeverPAIN' in an adult acute sore throat cohort (n=12,829), the '3C score' in an adult acute lower respiratory infection cohort (n=28,883), and the STARWAVe score in an acute cough and respiratory infection children's cohort (n=8,394). We calculated median odds ratios to quantify practice-level variation in prescribing rates, adjusted for illness severity.

Results: There was substantial variability in practice prescribing rates (ranges 0%-97%, 7%-100%, and 0%-75% in the three cohorts respectively). There was evidence that higher prescribing practices saw a higher proportion of unwell patients. At the individual level, more unwell patients were more likely to receive a prescription but prescribing levels for those with low scores were still high. The median odds ratio was 2.6 (95% CrI2.3-2.9) in the sore throat dataset, 2.9 (95% CrI 2.6-3.2) in the adult cough dataset and 2.1 (95% CrI 1.8-2.4) in the children's cough dataset.

Conclusion: Higher prescribing practices may see more unwell patients with high illness severity scores, but the differences in scores accounts for a minority of between practice prescribing variation. There is likely to be scope for further reductions in antibiotic prescribing among patients with low illness severity scores. Further research is needed to explore the additional factors which account for variation in prescribing levels.

Introduction

Acute uncomplicated respiratory tract infections are the commonest acute illness managed in primary care among developed countries and substantial numbers still receive antibiotics[1, 2]. However, systematic reviews have suggested that antibiotics confer limited symptomatic benefit for acute bronchitis[3] and sore throat[4]. Moreover prescribing promotes antibiotic resistance - which is dominated by primary care prescribing of antibiotics[5] and tackling antibiotic resistance is an international priority.

Analysis of routine prescribing data reveals wide variation in antibiotic prescribing rates between practices. In one large United Kingdom (UK) study using data from the Clinical Practice Research Datalink (CPRD),the median general practice prescribed antibiotics at 54% of respiratory tract infection (RTI) consultations, ranging from 39-69% in the lowest to highest decile of prescribing[1]. The rates observed in the The Health Improvement Network (THIN) database between 2013 and 2015 for acute bronchitis consultations suggested that 82% resulted in an antibiotic prescription and for sore throat 59% of consultations resulted in a prescription.[6] Whilst antibiotics are clearly appropriate and necessary in some cases, modelling suggests that the ideal prescribing rates for these conditions are much lower – 13% for both conditions.[6]

A recent paper exploring data from UK national prescribing datasets showed that although antibiotic prescribing rates have fallen since 2010, there is considerable geographic variation [7]. Higher prescribing practices tended to have a higher proportion of patients >65 years, a higher proportion of patients <18 years, a higher proportion of patients with long-term conditions, a higher level of deprivation and were more likely to be rural. The authors suggest that were all practices to prescribe at the lowest decile rate from 2017, 10.8 million fewer prescriptions could have been issued, a reduction of 34%.

Research in the THIN database also explored variability in antibiotic prescribing and found that a model including consultation rates, comorbidities, steroid and immunosuppressive use and demographics still could not explain the considerable amount of the between-practice variation.[8] A further study in national prescribing data similarly found that between-practice variation in prescribing rates could not be explained by legimate medical reasons, such as different prevalence of smoking, comorbidities,or deprivation. [9]

At the individual level, the decision to prescribe is a complex one[10]. General Practitioners (GPs) prescribe for a wide range of reasons, including psychosocial aspects[11]. The current guidelines suggest an immediate prescription for those at higher risk of complications due to comorbid conditions[12]. Many also prescribe for to reduce the risk of complications even though complications are rare, In sore throat, ~~and~~ the number needed to treat to reduce the risk of complications such as quinsy, impetigo, cellulitis, otitis media, and sinusitis, is nearly 200 ~~to reduce the complication risk~~[13]. In one interview study, GPs spoke of uncertainty about which patients were at most risk and would benefit most from an antibiotic prescription, and many acknowledged they had a different threshold for prescribing to patients with comorbidity or lower socioeconomic status[11].

Routine data cannot tell us whether the observed wide range in prescribing might be attributable to patient characteristics (case mix) or practice characteristics or culture. It may not be appropriate for all practices to aim to be prescribing in line with the lowest decile if, for example, some practices tend to see a larger proportion of patients who present with signs and symptoms that suggest they may benefit from antibiotics.

As electronic health record data does not provide information on the severity of infection, there is an advantage to instead exploring this question using cohort data. This paper reports a secondary analysis of three large primary care cohorts investigating acute respiratory infections, one in acute sore throat[13] and two in acute cough[14, 15]. These datasets included clinical data at the index consultation, thereby enabling further exploration of the relationship between patient (allowing us to stratify patients into high/low risk of poor prognosis) and practice factors in the prescribing decision.

Methods

Study populations

This was a secondary analysis of three large cohort studies. These cohorts were constructed to develop prediction rules to guide antibiotic treatment in a primary care context. Participating GPs were asked to document their normal prescribing practice and were aware that these practices would help the study teams to develop clinical prediction rules, but were not aware of which predictors would ultimately be included in these rules ~~and were instructed to follow their normal practice with respect to antibiotic prescribing.~~

The DESCARTE study (Decision rule for the Symptoms and Complications of Acute Red Throat in Everyday practice)[13] was prospective cohort study comprising 14,610 adults aged ≥16 years presenting with acute sore throat (≤2 weeks' duration). Patients were recruited from 616 practices in England and Wales between November 2006 and June 2009

The 3C study (cough complication cohort)[14] was a prospective cohort of 28 883 patients with lower respiratory tract infection recruited from 522 UK practices between 2009 and 2013.

The TARGET study[15] was a prospective cohort of 8394 children aged between 3 months and 16 years presenting with acute cough and respiratory tract infection recruited from 247 general practices in England between July 2011 and June 2013.

In all three studies, clinicians completed a case report form detailing clinical signs and symptoms at the initial consultation. In the 3C and TARGET studies, patient-level deprivation was measured by matching postcode to IMD 2010 data.[16] In the DESCARTE cohort, this information was not available at the individual level and the practice postal code was instead used to determine the IMD 2010 score.

Statistical methods

Descriptive statistics and graphs were used to explore whether participating practices with higher prescribing rates saw more patients who were likely to benefit from an antibiotic, as well as to summarised whether these patients were more likely to actually receive an antibiotic prescription. For the DESCARTE sore throat cohort, the FeverPAIN score includes fever during the previous 24 hours, pus on tonsils, attendance within 3 days of onset, severely inflamed tonsils and no cough or coryza[17]. In the UK, National Institute for Health and Clinical Excellence (NICE) guidelines suggest that those with a score of 0 or 1 might be unlikely to benefit from antibiotics whilst a score of 4 higher should be considered for an antibiotic prescription[18].

The Centor score is also available in the DESCARTE cohort and includes absence of cough, swollen and tender anterior cervical nodes, temperature > 38°C, tonsillar exudates, age.[19]. NICE guidance suggests that patients with a Centor score of 0, 1 or 2 are unlikely to benefit from antibiotics whereas those with a score of 3 or 4 should be considered for an immediate or delayed antibiotic [18]. Results for all analyses using the Centor score are given in the supplementary material (see Figure S1 and Table S1).

For the 3C cough cohort in adults, this was based on the risk of pneumonia, defined as having one of temperature >37.8°C, crackles on auscultation, oxygen saturation <95%, and pulse >100·min).[20]. Having at least one of these symptoms was associated with an increased risk of pneumonia on x-ray and therefore these patients should be considered for an immediate antibiotic.

For the TARGET cohort, children presenting with cough, we used the STARWAVe clinical rule. STARWAVe is comprised of short illness (≤3 days), temperature>37.8°C; age (<24 months); recession; wheeze; asthma; and vomiting[15]. Scores of 0/1 indicate very low risk of hospitalisation in the following 30 days and these children are unlikely to benefit from antibiotics. A score of 2-3 represents “normal” risk and again a strategy of no prescribing or delayed prescribing may be appropriate. Children with a score of 4 or more are considered high risk and should be considered for an immediate antibiotic prescription.

As practices recruiting few patients may have recruited selectively and provided limited participants for analysis we only included all practices which had recruited at least 10 patients into the study. We also exclude any patients who were referred to hospital on the same day as their consultation. In these patients it is less likely that a GP would issue a prescription, leaving the prescribing decision to the hospital clinicians. And we excluded those who received a delayed prescription. These represented too small a proportion of each cohort to explore the variability between practices.

The probability of receiving an antibiotic prescription was modelled in a multi-level logistic regression model. The model included as independent variables FeverPAIN score for sore throat (or the 3C score for pneumonia risk or STARWAVe score for risk in children), age, gender, deprivation score and co-morbidity. All variables were included in the way in which they had been collected in the original studies. Age was a continuous variable modelled linearly, deprivation used IMD quintiles and comorbidity defined as the presence of at least one comorbid condition. Practice was included as a random effect. We then calculated the median odds ratio (MOR) and 95% credible interval. This transforms the variability between practices into an odds ratio scale.[21, 22] ~~It describes the probability that two randomly selected practices would treat an identical patient in the same way~~ It describes the increase in odds of receiving a prescription as a patient moves from a lower-risk cluster to a higher-risk cluster. ~~.~~A MOR of 1.00 would indicate no variability between practices, a significant score >1 would suggest that some practices are more likely to treat than others, irrespective of patient severity.

To obtain the MOR and credible interval, we ran the model using MCMC estimation via the "runmlwin" command[22] in Stata v14.0. This directly computes the 95% credible interval for the MOR using the posterior distribution of the area variance.

We also calculated the proportion of the variance explained by the variables in the model. ~~Whilst this value, usually denoted R^2 is automatically available for linear regression, for multi-level logistic regression, it must be calculated from the residual variances. We therefore calculated the R^2 value as:~~ $\cancel{R^2 = \frac{Var_{null} - Var_{full}}{Var_{null}}}$ ~~where Var_{null} is the residual variance of a null model with only the intercept and practice-level random effects, and Var_{model} is the residual variance of a model that the independent variables and the practice-level random effect.~~ We have followed the approach set out in Weinmayr *et al*[23] and calculated the relative reduction in the rescaled tau parameter compared to the null model using the Stata do-file provided as supplementary material to their paper.

It is possible that differences in prescribing rates at the practice level may reflect differences not in routine prescribing but in the way in which GPs recruited into the cohort studies. Although GPs were asked to recruit all eligible patients with sore throat/cough, it is possible that some might have opted to only include those patients to whom they planned to prescribe. If different GPs interpreted the inclusion criteria in different ways, we would see a wider range of prescribing rates and more variability between practices than exists in routine practice. To test this assumption, we matched practices from the 3C cohort to their overall antibiotic prescribing rates based on Specific Therapeutic group Age-sex weightings Related Prescribing Units (STAR-PU) from 1 January to 31 December 2015 available at the practice level from the NHS England Antibiotic Quality Monitoring Dashboard[24]. Due to the way in which the data was collected it was not possible to do this for the DESCARTE or TARGET cohorts. We hypothesised that a high correlation between the prescribing rate in the cohort and the prescribing rate in the national data would indicate that practices had not selectively recruited into the cohort but that the prescribing rate in the data was reflective of normal practice.

Results

Study population

After excluding those practices that recruited less than 10 participants to the studies, those hospitalised on the day and those who received a delayed prescription, there were 9,007 participants in the DESCARTE cohort, 24,320 in the 3C cohort and 7,252 in the TARGET cohort.

The datasets represented somewhat different populations, which reflects both the illness of interest and their target populations. The DESCARTE sore throat cohort was 67.4% female with an average age of 33.64 years. Most participants had been unwell for around 4 days prior to consultation. The 3C cough cohort was 59.2% female and had a higher average age of 51.87 years. Most participants had been ill for slightly longer – 7 days = prior to their initial consultation. The TARGET cohort recruited only children with acute and this is reflected in the lower average age of 3.81 years and a somewhat shorter duration prior to consultation of 5 days, compared to the 7days for the adult 3C cough cohort.

The median IMD rank was 15,780 (IQR 6636,24189) in the DESCARTE data and 16,590 (IQR 8393, 25311) in the TARGET data. IMD ranks range from 1 in the most deprived Lower Super Ouput Area to 32,844 in the least deprived area, suggesting that out population was recruited from practices with a range of deprivation levels[25]. This data was not available for 3C, where data was only recorded in deprivation quintiles.

Variation in prescribing rates at the practice level

There was substantial variability in prescribing rates by practice (Table 1). In the sore throat dataset, the range was 0%-97% of patients receiving an immediate antibiotic prescription, with a median rate of 46%. In the 3C dataset the range was 7%-100%, with a median rate of 62% and in TARGET the range was 0%-75% with a slightly lower median rate of 22%.

The correlation between the practices in the 3C dataset and their antibiotic prescribing rates in the national data was 0.84 suggesting that high prescribers in the cohort were very likely to be high prescribers in the national data. Therefore it is likely that these wide ranges of prescribing rates are indicative of true differences between practices and are not an artefact of their interpretation of the study recruitment procedures.

There was some evidence in all 3 datasets that those practices with higher prescribing rates saw more patients with higher severity/prognostic scores. There was a moderate correlation of 0.42 for the FeverPAIN score and prescribing rate, in the sore throat dataset. In the adult cough dataset, the correlation was 0.44 between pneumonia risk and the prescribing rate. The correlation was lower in children at only 0.20. If practices were divided into quartiles by prescribing rate then, as Figures 1-3 illustrate, there is a gradient, with the higher prescribing quartile tending to see more patients who were likely to benefit from a prescription.

Prescribing rates at the individual patient level

At the individual level, patients who were more unwell are more likely to receive a prescription with 96.9% of those with a FeverPAIN score of 4+ receiving an immediate antibiotic (Table 2). The proportion was similarly high for those with a higher risk of pneumonia, with 91.7% receiving an immediate antibiotic. But prescribing levels for those will low risk scores was also high; ~~–~~ 38.7% of those with a FeverPAIN score of 0/1 received a prescription and 43.4% of those at low risk for pneumonia.

In children there seemed to be more uncertainty around prescribing, with only 66.2% of children in the highest risk group receiving a prescription. However, as in the adult datasets, a high proportion – 26.4% of those at very low risk of future admission – still received a prescription.

Median Odds ratios

The median odds ratio was high in all the datasets. In the sore throat dataset, the MOR 2.49 (95% credible interval 2.21, 2.85) when the model included FeverPAIN score, age, sex, deprivation and comorbidity. These individual level variables only reduced the rescaled tau^2 parameter by 3.2%, suggesting that the proportion of variability between practices~~accounted for 12.6% of the variance~~ in the probability of receiving a prescription explained by the individual level variables is low. The MOR was 2.86 (95% credible interval 2.60, 3.17) in the adults cough dataset and the independent variables ~~accounted~~ reduced the the rescaled tau^2 ~~for~~by 0.8% ~~of the variability.~~ And in the children's cough dataset, the MOR was 2.06 (95% credible interval 1.82, 2.36) and the individual level variables ~~accounted for~~reduced the rescaled tau^2 by~~1.9~~3.6% ~~of the variability~~. This suggests that even after controlling for risk score, age, sex, deprivation and comorbidity, an identical patient attending 2 randomly selected practices would be much more likely to receive antibiotics in some practices than in others and that there is substantial variability which is not explained by the variables in the model.

Discussion

Summary of main findings

There was a large range in prescribing in this observational data set in line with expectations from analysis of routine data. In adults, antibiotics were targeted to those who were more unwell however there was wide variation in prescribing to less unwell patients. In children, the pattern was similar but there seemed to be more uncertainty in the higher risk children as well, with only 66% receiving an immediate prescription.

Whilst some of that variation in prescribing can be attributed to illness severity (case mix) there was evidence that there was considerable residual variability, attributable to practice and physician factors.

Findings in context of existing literature

Our study is consistent with the findings of other work in the United Kingdom and the United States which has shown high levels of variability in prescribing between practices. Palin *et al.* explored variability in antibiotic prescribing at the GP practice level in the CPRD database over time.[26] They also found considerable between-practice variability, with some practices prescribing 10% of the time and others up to 70% of the time. Patient characteristics did not completely explain this variability, nor did changes in prescribing guidelines over time. Several studies have suggested that age, region, race and comorbid conditions are associated with antibiotic prescribing.[7, 27-29]. But all these studies all concluded, as we did, that there was considerable variability between practices that could not be explained by these factors alone and that there remained considerable opportunity for reducing inappropriate prescriptions

There is also evidence that high levels of antibiotic prescribing are associated with high levels of antidepressant prescribing[30]. And recent studies have shown that the levels of steroid and immunosuppressive drug prescribing[8], and the levels of prescribing of other medications including non-opioid painkillers and benzodiazepines [31] were stronger predictors of antibiotic prescribing rates than variables such as comobidities or deprivation. ~~and i~~It is possible that some GPs and/or practices have a lower threshold for prescribing than others. Further work may be needed to address this propensity to prescribe, given the evidence from our dataset that it may not be driven by patient-level factors or the likelihood of the prescription providing a benefit.

Strengths/limitations

Data is available for three large cohorts with prospective collection of baseline signs/symptoms enabling an analysis including illness severity. Whilst other studies have been able to explore variability in prescribing in routine data, baseline signs and symptoms are often poorly recorded. It is therefore a strength of this study that we were able to look at the potential of these factors to explain variability in prescribing across three large datasets. We were also able to control for the baseline severity of the illness which may be a potential source of residual confounding by indication in electronic health record studies.

We cannot exclude selection bias where GPs may have chosen selected patients for entry into the study with a potential impact on the attributed prescribing rates. However all three cohorts revealed similar findings and for 3Cs, we were able to compare practice level prescribing in the cohort to national antibiotic prescribing data from 2015; the correlation with national prescribing rates in the cohort study was high (r=0.84). We cannot exclude the possibility that high prescribing practices systematically attribute symptom scores with higher severity hence explaining the greater illness severity observed in these sites but we would have hypothesised that this would have reduced the variability as higher prescribing would be better explained by higher severity scores.

We classified practices into quartiles based on their prescribing rates. However, these quartiles are based on the distribution in the data. Therefore “low” and “high” prescribing practices are designations relative to other practices in the dataset, regardless of whether their rates of prescribing were high or low in real terms or whether their prescribing rates were appropriate to the patients they saw.

The cohorts collected between 2006 and 2013. It is possible that over time prescribing generally has changed and/or that the publication of the rules derived from these datasets may have improved the appropriateness of prescribing. For example, FeverPAIN is now included in the NICE guidelines but this change occurred during the time that the sore throat cohort was collecting data. Whilst it is possible that prescribing has moved on from the picture provided by this data, as noted above the results in this paper are consistent with other recent studies using routine data which have observed similar variability in prescribing.

We could only explore the relationship between those characteristics that were measured in the cohort studies and prescribing. It is possible that better recording of the data, e.g. more data on comorbid conditions or household deprivation, might have helped to explain a larger proportion of the variance. However, as discussed below, other studies have found a similar results. Important factors such as the experience of the GP, social factors or whether or not the patient requested an antibiotic were not recorded and may have helped to explain some of the variation observed. Whilst there is robust evidence for lack of benefit of antibiotics for symptom relief in adults with sore throat and bronchitis the same is not the case in children where are no substantive studies of antibiotics for Lower Respiratory Tract Infection (LRTI). We used the newly developed STARWAVE tool to attribute prescribing benefit, however this was developed to predict children at risk of admission with RTI and we do not know if antibiotics modify this risk or if other groups of children might potentially benefit from antibiotics.

Implications for clinical practice and further research

Higher prescribing practices did see more severely unwell patients and therefore caution should be exercised in targeting those practices specifically. Antibiotics are appropriate and even necessary for some patients and whilst there may be ideal levels of prescribing overall for different conditions the differences observed in the patient populations at different practices in this study and others suggest that setting a the same practice-level target for all practices is unlikely to be appropriate [6, 9, 27].

The ‘low hanging fruit’ for antibiotic stewardship is those patients at low risk of serious infection or who are not very unwell. Instead of targeting practices to reduce prescribing, encouraging practitioners to use clinical scores to limit prescribing for patients with less severe illness could yield substantial reductions in antibiotic prescriptions. For acute sore throat and LRTI the overall risk of complications is low. Whilst the use of clinical scores may not predict the likelihood of future complications, such scores are a useful guide to prescribing when coupled with clinical judgement –FeverPAIN, for example, whilst not a predictor of complications[32] but is a good predictor of Strep infection and hence need for antibiotics[17]. Similarly the 3C score was developed to predict pneumonia, which would usually be treated with antibiotics. The PPV of having one of these signs was 20%, which again may represent a suitable population for targeted prescribing[21]. The STARWAVe score helped to identify the 11.8% of children in the highest risk category who were at high risk of future admission. Whilst not all would have benefited from a prescription, this group might be the most suitable to targeted prescribing”[15].

Further guidance on how to recognise children at high risk of adverse outcome may also help to ensure that antibiotics are targeted more appropriately in this population.

Whilst this study has highlighted that illness severity scores and individual characteristics explain very little of the variability in practice-level prescribing, further research is needed to explore which factors do help to explain these observed differences. This may help to better target interventions to reduce prescribing in higher prescribing practices.

Acknowledgements

Funding

This study was carried out as part of our routine work and represents a secondary analysis of existing data. However the original collection and analyses of the data was funded as follows:

The DESCARTE cohort was funded by the UK Medical Research Council

The 3C cohort was funded by the National Institute for Health Research (NIHR) under its programme grants for applied research programme (reference No RP-PG-0407-10098).

The TARGET cohort was funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0608-10018).

ADH holds a NIHR Senior Investigator Award (NIHR200151). The views expressed are those of the authors and not necessarily those of the NIHR, the funder of the original cohort studies, or the Department of Health and Social Care

In all cases the views expressed are those of the authors and not necessarily those of the NHS, the funder of the original cohort studies, or the Department of Health and Social Care.

Transparency Declaration

None of the authors have any conflicts of interest to declare.

References

1. Gulliford MC, Dregan A, Moore MV et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *BMJ Open* 2014; **4**.

For peer review only

2. Hawker JI, Smith S, Smith GE et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations.

3. Smith SM, Fahey T, Smucny J et al. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2014; **3**: CD000245.

4. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2013; **11**: CD000023.

5. Goossens H, Ferech M, Vander Stichele R et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**: 579-87.

6. Pouwels KB, Dolk FCK, Smith DRM et al. Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. *Journal of Antimicrobial Chemotherapy* 2018; **73**: 19-26.

7. Curtis HJ, Walker AJ, Mahtani KR et al. Time trends and geographical variation in prescribing of antibiotics in England 1998–2017. *Journal of Antimicrobial Chemotherapy* 2018: dky377-dky.

8. Pouwels KB, Dolk FCK, Smith DRM et al. Explaining variation in antibiotic prescribing between general practices in the UK. *J Antimicrob Chemother* 2018; **73**: ii27-ii35.

9. Hope EC, Crump RE, Hollingsworth TD et al. Identifying English Practices that Are High Antibiotic Prescribers Accounting for Comorbidities and Other Legitimate Medical Reasons for Variation. *EClinicalMedicine* 2018; **6**: 36-41.

10. Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. *Journal of Antimicrobial Chemotherapy* 2011; **66**: 2215-23.

11. Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. *BMJ* 2003; **326**: 138.

12. NICE. Prescribing of antibiotics for self limiting respiratory tract infections in adults and children in primary care. . *(Clinical guideline 69) wwwniceorguk/CG69* 2008.

13. Little P, Stuart B, Hobbs FD et al. Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study. *Lancet Infect Dis* 2014; **14**: 213-9.

14. Little P, Stuart B, Smith S et al. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. *BMJ* 2017; **357**: j2148.

15. Hay AD, Redmond NM, Turnbull S et al. Development and internal validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. *The Lancet Respiratory Medicine* 2016; **4**: 902-10.

16. The English Indices of Deprivation 2010. In: government Docal, ed, 2011.

17. Little P, Moore M Fau - Hobbs FDR, Hobbs Fd Fau - Mant D et al. PRImary care Streptococcal Management (PRISM) study: identifying clinical variables associated with Lancefield group A beta-haemolytic streptococci and Lancefield non-Group A streptococcal throat infections from two cohorts of patients presenting with an acute sore throat.

18. Public Health England. Sore throat (acute): antimicrobial prescribing. In: NICE guideline, ed. https://www.nice.org.uk/guidance/ng84/resources/sore-throat-acute-antimicrobial-prescribing-pdf-1837694694085, 2018.

19. Fine AM, Nizet V, Mandl KL. Large-scale validation of the centor and McIsaac scores to predict group a streptococcal pharyngitis. . *Arch Intern Med* 2012; **172**: 5.

20. Moore M, Stuart B, Little P et al. Predictors of pneumonia in lower respiratory tract infections: 3C prospective cough complication cohort study. *Eur Respir J* 2017; **50**.

21. Larsen K, Petersen JH, Budtz-Jorgensen E et al. Interpreting parameters in the logistic regression model with random effects. *Biometrics* 2000; **56**: 909-14.

22. Merlo J, Chaix B, Ohlsson H et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *Journal of epidemiology and community health* 2006; **60**: 290-7.

Confidential: For Review Only

23. Weinmayr G, Dreyhaupt J, Jaensch A et al. Multilevel regression modelling to investigate variation in disease prevalence across locations. *International Journal of Epidemiology* 2016; **46**: 336-47.

24. England N. Antibiotic quality premium monitoring dashboard. https://www.england.nhs.uk/publication/antibiotic-quality-premium-monitoring-dashboard/, 2018.

25. 2010 TEIoD. 2011.

26. Palin V, Mölter A, Belmonte M et al. Antibiotic prescribing for common infections in UK general practice: variability and drivers. *Journal of Antimicrobial Chemotherapy* 2019.

27. Smith DRM, Robotham JV, Dolk FCK et al. Explaining variation in antibiotic prescribing between general practices in the UK. *Journal of Antimicrobial Chemotherapy* 2018; **73**: ii27-ii35.

28. Jung S, Sexton ME, Owens S et al. Variability of Antibiotic Prescribing in a Large Healthcare Network Despite Adjusting for Patient-Mix: Reconsidering Targets for Improved Prescribing. *Open Forum Infectious Diseases* 2019; **6**.

29. Fleming-Dutra KE, Hersh AL, Shapiro DJ et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011Inappropriate Antibiotic Prescriptions Among Ambulatory Care Visits, 2010-2011Inappropriate Antibiotic Prescriptions Among Ambulatory Care Visits, 2010-2011. *JAMA* 2016; **315**: 1864-73.

30. Spence R RA, Ariti C and Bardsley M. Focus on: Antidepressant prescribing. Research report. *Nuffield Trust and Health Foundation* (2014).

31. Li Y, Mölter A, White A et al. Relationship between prescribing of antibiotics and other medicines in primary care: a cross-sectional study. *Br J Gen Pract* 2019; **69**: e42-e51.

32. Little P, Stuart B, Hobbs FDR et al. Predictors of suppurative complications for acute sore throat in primary care: prospective clinical cohort study. *BMJ : British Medical Journal* 2013; **347**: f6867.

TABLES AND FIGURES

Table 1. Baseline characteristics

Participant characteristics	DESCARTE	3C	TARGET
Female	6071 (67.4%)	14,392 (59.2%)	3484/7252 (48.0%)
Mean age in years (s.d.)	33.84 (14.61)	51.87 (17.98)	3.81 (3.72)
Mean temperature °C (s.d.)	36.83 (0.70)	36.73 (0.66)	36.98 (0.77)
Median days of illness prior to consultation (IQR)	4 (2,6)	7 (5,14)	5 (3,10)
Practice characteristics			
Number of practices recruiting 10+ patients	222	363	135
~~Mean Index of Multiple Deprivation~~	~~21.3 (15.0)~~ 15785 (6636, 24189)	~~20.8 (14.8)~~ N/A	~~20.5 (14.2)~~ 16590 (8393, 25311)

Confidential: for peer review only

~~score~~Median Index of Multiple Deprivation rank			
Range of antibiotic prescribing rate	0%-97%	7%-100%	0%-75%
Median antibiotic prescribing rate (LQ, UQ)	46% (37%, 61%)	62% (47%, 75%)	22% (15%, 32%)

Figure 1. FeverPAIN score by prescribing quartile

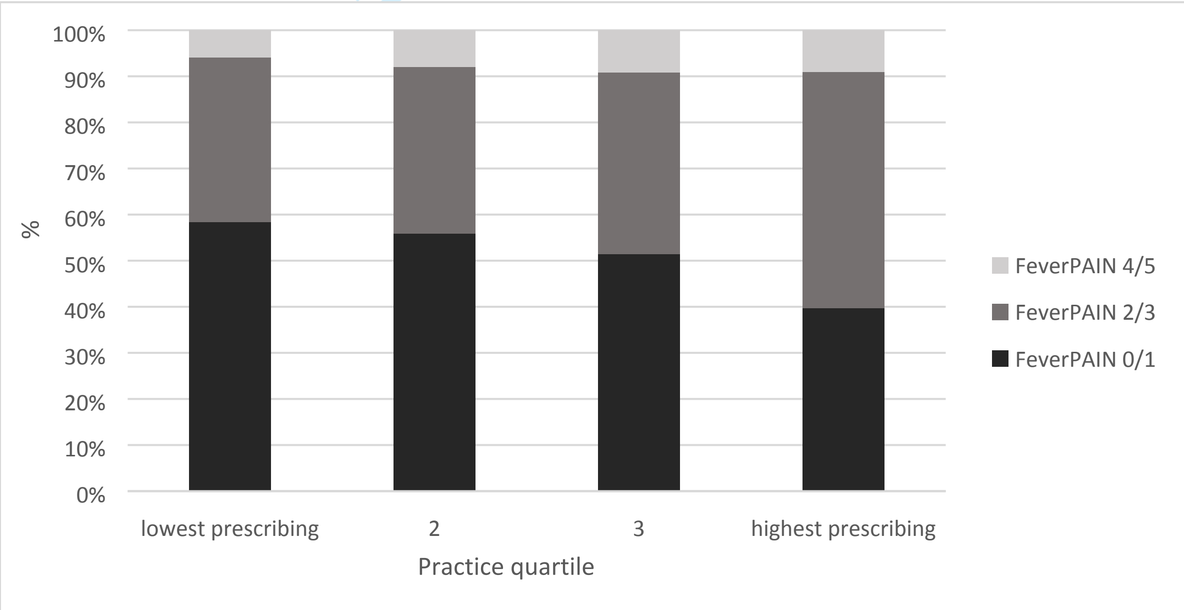


Figure 2. Pneumonia risk by prescribing quartile – 3C cohort

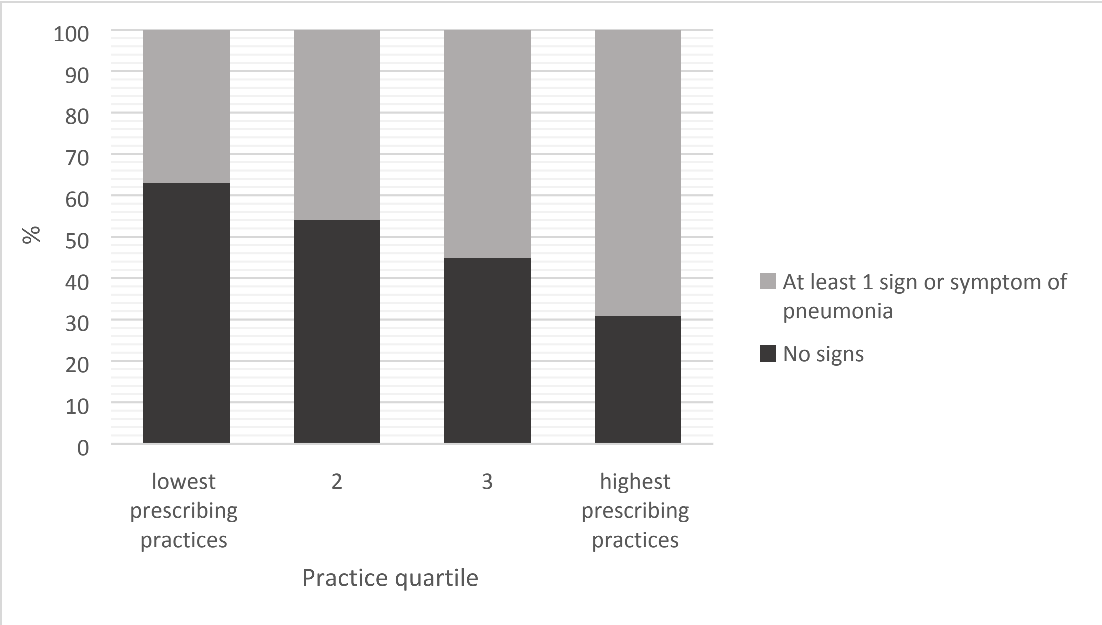


Figure 3. STARWAVe score by prescribing quartile – TARGET cohort

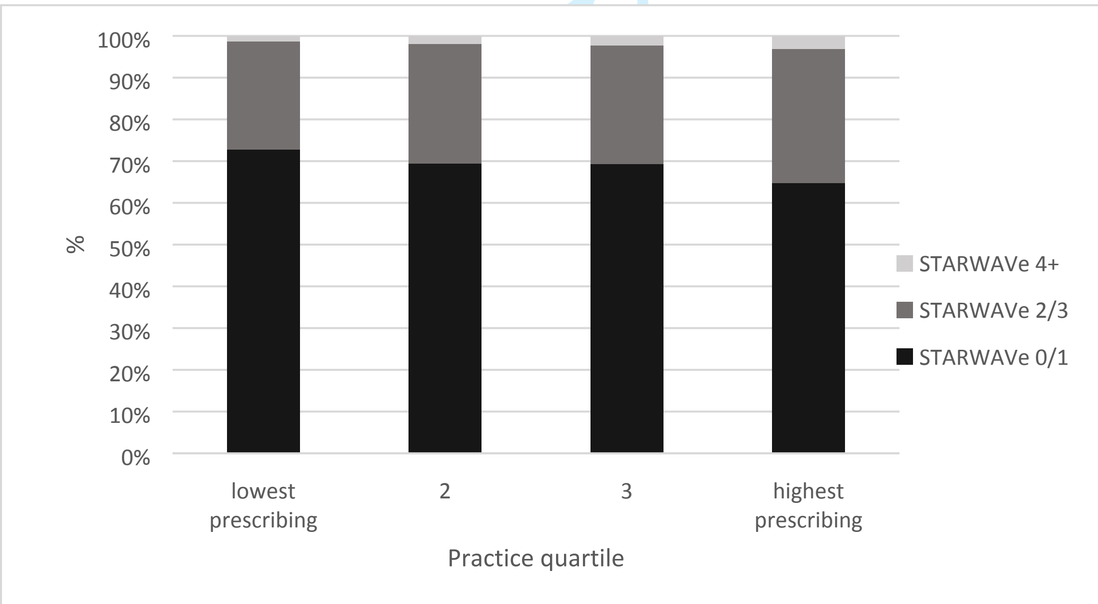


Table 2. Proportion receiving immediate antibiotics by FeverPAIN, pneumonia risk and STARWAVe scores

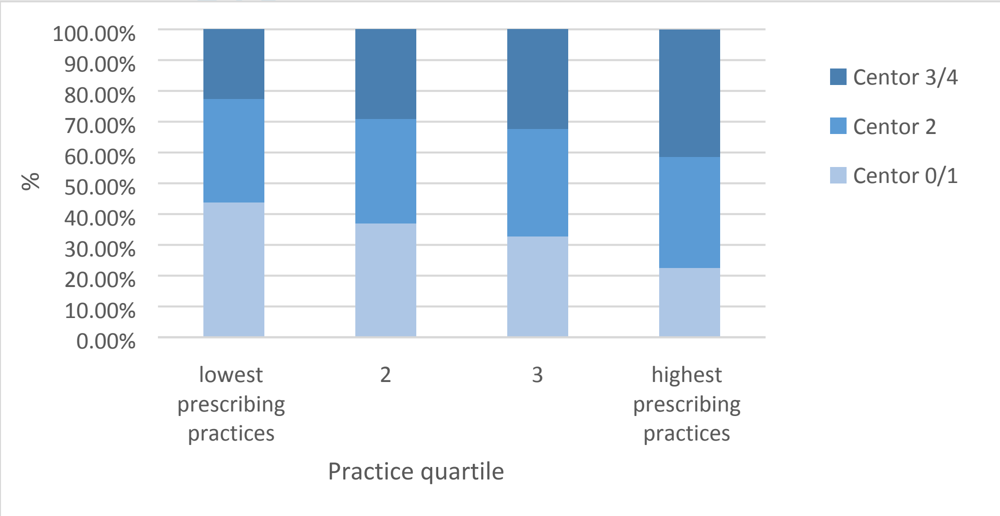
Received immediate antibiotics	FeverPAIN score			Pneumonia score		STARWAVe score		
	0/1	2/3	4/5	No signs	1+ signs	0/1	2/3	4+
No	2,685 (61.3%)	1,052 (30.6%)	24 (3.1%)	6069 (56.6%)	1,127 (8.3%)	3664 (73.6%)	1312 (61.9%)	51 (33.8%)
Yes	1,693 (38.7%)	2,391 (69.5%)	7,58 (96.9%)	4662 (43.4%)	12,462 (91.7%)	1314 (26.4%)	810 (38.1%)	100 (66.2%)

Confidential: for peer review only

Supplementary Data

The results for Centor were similar to those for FeverPAIN, with higher prescribing practices seeing a higher proportion of unwell patients. There was a moderate correlation of 0.50 between Centor score and prescribing rate in the sore throat dataset.

Figure S1 Centor score by prescribing quartile



At the individual level, more severely ill patients are more likely to receive a prescription with 90.7% of those with a Centor score of 3+ receiving an immediate antibiotic (Table 2). But prescribing levels for those will low severity scores was also high – 29.5% of sore throat patients with a Centor score 0 or 1 received a prescription. For those with a Centor score of 2, the probability of receiving a prescription was almost 50/50.

Table S1 Proportion receiving immediate antibiotics by Centor score

Received immediate antibiotics	**Centor score**		
	0/1	2	3/4
No	2,147 (70.5%)	1,501 (50.7)%	278 (9.3%)
Yes	900 (29.5%)	1,460 (49.3)%	2,721 (90.7%)

The MOR was 2.56 (95% credible interval 2.26, 2.94) when the model included the Centor score.

Confidential: for peer review only